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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,806	10/03/2008	Daniel Harari	HARARI 1	7157

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	PAPER NUMBER
1646	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,806	HARARI, DANIEL	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,4,5,11,12 and 14-42* is/are pending in the application.

5a) Of the above claim(s) *5,15-31 and 33-40* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,4,11,12,14,32,41 and 42* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *2/21/2006 and 10/25/2010* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's amendment of the claims filed 31 May 2011 has been entered. Applicant's remarks filed 31 May 2011 are acknowledged.

Election/Restriction

Applicant traverses the Election/Restriction on the basis that the specified sequences in claim 1 (i.e., SEQ ID NOs: 74-84, 93, 95, 104, 109 and 110) share a common structure, as well as a common function and effects; thus, these variants have a special technical relationship that unifies them in PCT practice. Applicant argues that the common structure is a truncated EGF domain having only the first four (of six) conserved cysteines found in an intact EGF domain; the variants end one amino acid after the fourth conserved cysteine; the truncated EGF domain of the variants contains a consensus sequence that can be represented as follows: (X-8)-Cys-(X-7)-Cys-(X-2 to 3)-Gly-X-Cys-(X-10 to 13)-Cys-X, where X is any sequence of the relevant number of amino acids. Applicant argues that the common function and effect is an inhibitory activity on ErbB receptor-mediated signaling. Applicant argues that one particular

activating ligand is typically associated with more than one receptor and activates several different ErbB receptor complexes or combinations; it is contemplated that the inhibitory ligands work in a similar way, namely, one inhibitory ligand may exert an inhibitory activity towards more than one receptor; thus inhibiting ErbB-receptor mediated signaling.

Applicants' argument has been fully considered but has not been found to be persuasive.

As set forth in the previous Office Actions, the Requirement for Restriction Election is proper because the polypeptides represented by different SEQ ID NOs are drawn to multiple distinct products which have different structures and functions. The PCT rules do not provide for the examination of multiple products in one application. The amino acid sequences shown in the SEQ ID NOs represent splicing variants of different ErbB family ligands, including NGR, EGF, TGF-alpha, betacellulin, amphiregulin, HB-EGF, epiregulin, epigen, etc. These molecules not only differ in the amino acid sequences, but they are derived from structurally distinct ErbB ligand genes. Applicant argues that these molecules contain a consensus sequence, however, in the consensus sequence described above, only 5 amino acids are defined, compared to a full length ErbB ligand protein of approximately 200 amino acids. Such limited structural similarity does not satisfy as "a common significant structural element". Further, the claimed splicing variants have a materially different design, mode of operation, function, or effect. Although all ErbB ligand family proteins function in the ErbB receptor-mediated signaling pathways, however, it is well known in the art that different ErbB ligands bind

to different receptors, activate different signaling pathways, and mediate different downstream effects. Furthermore, there is nothing of record to show the splice variants of different ErbB ligands of the instant application to be obvious variants. Should Applicant traverse on the ground that the inventions are not patentably distinct, Applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Claim 2, 3, 6-10 and 13 are cancelled. Claim 42 has been added. Claims 1, 4, 5, 11, 12 and 14-42 are pending. Claims 5, 15-31 and 33-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claims 1, 4, 11, 12, 14, 32, 41 and 42 are under examination to the extent they read on the elected invention of splicing variant SEQ ID NO: 81.

Claim Objections Withdrawn

The objection to claims 8 and 9 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, is withdrawn in response to Applicant's cancellation of the claims.

The objection to claim 1 for informalities is withdrawn in response to Applicant's amendment of the claim.

Claim Objections

Claims 1, 4 and new claim 42 are objected to for reciting non-elected inventions (i.e., sequences other than SEQ ID NO: 81).

Applicant traverses the Election/Restriction and argues that generic claims recite the common structure and activity and are allowable.

As set forth above, the Requirement for Restriction Election is proper because the polypeptides represented by different SEQ ID NOs are drawn to multiple distinct products and the PCT rules do not provide for the examination of multiple products in one application.

Claim Rejections Maintained/New Grounds of Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The amended and newly added claims 1, 4, 11, 12, 14, 32, 41 and 42 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The basis of this rejection is as set forth in the previous Office Actions and the following.

Applicant argues that claim 1 as amended refers to a polypeptide comprising a splice variant of an ErbB ligand, where the C-terminal portion of the variant contains a selected SEQ ID NO and the N-terminal portion of the variant contains a sequence having at least 90% homology to the corresponding N-terminal sequence found in the known (activating) ErbB ligand from which the splice variant is derived. Applicant argues

that the EGF domain of the variant (which is part of the C-terminal portion) is truncated - it ends one amino acid after the fourth conversed cysteine, which is also the penultimate amino acid of the polypeptide; and the N-terminal flanking sequence of a certain splice variant is not derived from the N-terminal sequence of any known ErbB ligand, but rather from the specific known ligand from which that splice variant is derived. Applicant argues that the specification (page 65) provides the accession numbers of the corresponding known ligands, and a skilled artisan can readily find information about the sequences found upstream to the first conserved cysteine of the EGF domain using these accession numbers. Applicant further argues that determination of conservative amino acid substitutions that would maintain the properties of the splice variant are within the capabilities of a skilled artisan, in particular in view of the guidance provided in page 18 lines 24-33 and in the paragraph bridging pages 24 and 25; thus, a skilled artisan can envision the overall structure of the encompassed polypeptide and prepare it accordingly.

Applicants' argument has been fully considered but has not been found to be persuasive.

Independent claim 1 has been amended to recite *an isolated polypeptide comprising a splice variant of an ErbB ligand with the sequence set forth in SEQ ID NO: 81* (the elected splice variant), *the splice variant of an ErbB ligand comprising a truncated EGF domain having only the first four of the six conserved cysteines found in an intact EGF domain, wherein the fourth cysteine in said truncated EGF domain is the penultimate amino acid at the C terminus of the polypeptide, wherein the N-terminal*

flanking sequence of said splice variant of an ErbB ligand preceding the first cysteine of the EGF domain is at least 90% homologous to the corresponding N- terminal sequence found in the known ErbB ligand from which the splice variant is derived, and wherein said splice variant of an ErbB ligand exerts inhibitory activity on ErbB receptor-mediated signaling.

The claims as amended now require the splice variants exhibiting a specific function/activity, "*wherein said splice variant of an ErbB ligand exerts inhibitory activity on ErbB receptor-mediated signaling*". Although a skilled artisan can envision a genus of splice variants where the C-terminal portion of the variant contains the amino acid sequence of SEQ ID NO: 81, and the N-terminal portion of the variant contains a sequence having at least 90% homology to the corresponding N-terminal sequence found in the known (activating) ErbB ligand from which the splice variant is derived, however, a skilled artisan cannot envision from among the genus, which splice variants exert inhibitory activity on ErbB receptor-mediated signaling. Using the selected ErbB ligand splice variant as an example, SEQ ID NO: 81 is a truncated EGF domain derived from heparin binding-EGF (HB-EGF). The structure of a full-length HB-EGF is illustrated in Figure 1 of Luk'yanov et al. (Mol. Biology, 2002, Vol. 36(1):58-64, reference attached herein). A full-length transmembrance HB-EGF is 208 amino acids in length, including signal peptide, propeptide, secreted (mature) HB-EGF, transmembrane domain, and cytoplastic domain. The secreted (mature) HB-EGF domain is composed of a heparin-binding domain followed by an EGF domain that contains six cysteines forming three disulfide bonds. Luk'yanov et al. teaches a short form of HB-EGF (SF HB-EGF) which

has an altered EGF domain. Specifically, the SF HB-EGF contains only the first four of the six conserved cysteines, following the fourth cysteine is a stretch of 9 amino acids (i.e., the SF HB-EGF has exactly the same N-terminal sequence as the native HB-EGF and contains only the first four of the six conserved cysteines) (see Figure 1 of Luk'yanov et al.). However, Luk'yanov et al. showed that the SF HB-EGF has a mitogenic effect (a downstream activating effect of an ErbB signaling pathway), stimulating DNA synthesis in resting mammalian cells similar to HB-EGF. In other words, SF HB-EGF does not exhibit inhibitory activity on ErbB receptor-mediated signaling. Another example is a heregulin splicing variant, HRG-γ, taught by Eppenberger et al. (WO 99/14323) (reference provided previously). HRG-γ is characterized by a truncation in the EGF domain and the protein ends one amino acid after the fourth cysteine. Eppenberger et al. showed the biological activities of HRG-γ as being "inactive" in the ErbB receptor activation (which is different from an inhibitory activity, i.e., dominant negative activity). In fact, the specification does not contain examples showing any particular ErbB ligand splice variant exhibiting an inhibitory activity on ErbB receptor-mediated signaling. The specification shows that EGF(1-32) (SEQ ID NO: 77) and NRG2(1-32) (SEQ ID NO: 74) were inactive in potentiating mitogenesis, and exhibited weak or no binding to the ErbB receptor betacellulin. No data shows the inhibitory activity on ErbB signaling pathway. If the structural elements that result in the conversion of the splice variant from an agonist to an antagonist (as in the case of the truncated HB-EGF) reside in the N-terminal flanking sequence (e.g., mutations in the N-terminal flanking sequence render the polypeptide to exhibit the

inhibitory or dominant negative activity), the specification fails to disclose where and what these mutations are. There are no teachings regarding the correlation of structure to function.

With regard to new claim 42, although claim 42 does not recite the N-terminal flanking sequence limitation, the open-ended phrase "comprising" reads on that additional sequence(s) can be added to the splice variant.

Obviously, in the absence of more information with regard to the correlation of structure to function, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides. Therefore, the claims do not meet the written description provision of 35 U.S.C. §112, first paragraph, as the specification fails to provide sufficient distinguishing identifying characteristics for the polypeptides that exert inhibitory activity on ErbB receptor-mediated signaling.

Claims 1, 4, 11, 12, 14, 32, 41 and 42 are further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

With regard to the enablement rejection set forth in the previous Office Action, Applicant provides exactly the same arguments as stated above. Applicant argues that

given the guidance from the specification, a skilled artisan can envision the overall structure of the encompassed polypeptides and prepare them accordingly.

Applicants' argument has been fully considered but has not been found to be persuasive.

As discussed above, the specification fails to provide sufficient distinguishing identifying characteristics for the splice variant polypeptides that exert inhibitory activity on ErbB receptor-mediated signaling, and there is no sufficient guidance with regard to the correlation of structure to function. A skilled artisan cannot envision from among the genus of splice variants (which C-terminal portion contains the amino acid sequence of SEQ ID NO: 81, and the N-terminal portion contains a sequence having at least 90% homology to the corresponding N-terminal sequence found in the known (activating) ErbB ligand from which the splice variant is derived), which splice variants exert inhibitory activity on ErbB receptor-mediated signaling. Accordingly, one of an ordinary skill in the art would not know how to make these molecules.

Applicant argues that determination of conservative amino acid substitutions are within the capabilities of a skilled artisan, and further points out various sections in the specification for guidance, however, making conservative amino acid substitutions would not be sufficient to make a splice variant having an inhibitory or dominant negative activity, as these changes generally would not alter the properties of a polypeptide. Also, the cited sections of the specification describe conservative amino acid substitutions that result in a functionally equivalent ErbB ligand, not an inhibitory molecule. There is no guidance with regard to the amino acid changes that can make

an ErbB ligand splice variant exhibiting an inhibitory activity on ErbB receptor-mediated signaling. Such teachings regarding the structure/function correlation is critical, particularly in view of the structurally similar ErbB ligand splice variants, such as SF HB-EGF and HGR-γ described above in Luk'yanov et al. and Eppenberger et al., which do not exhibit an inhibitory activity on ErbB receptor (on the contrary, SF HB-EGF has mitogenic activity and stimulates ErbB receptor-mediated signaling).

In the absence of the detailed structural information for the genus of molecules, one of an ordinary skill in the art would not know how to make the polypeptides as claimed. Further, without the teachings regarding the correlation of structure to function, a skilled artisan has to screen a large number of polypeptides and determine their activity as an ErbB receptor antagonist. It would require tremendous undue experimentation, and does not satisfy the enablement requirement of 35 U.S.C. 112, first paragraph that stipulates one of ordinary skill in the art to make and use the invention, rather than "make and test".

Due to the large quantity of experimentation necessary to generate a large number of the splicing variant polypeptides recited in the claims, and determine their activity/function and uses, the lack of direction/guidance presented in the specification, the absence of working examples, the complex nature of the invention, the state of the art which fails to provide compensatory guidance, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 42 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 42 recites the broad recitation "*the splice variant of an ErbB ligand comprising a truncated EGF domain* ...", and the claim also recites "*a splice variant of an ErbB ligand consisting of a sequence*..." which is the narrower statement of the range/limitation. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Xiaozhen Xie/
September 19, 2011